CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-757/S-021

Administrative Documents

sanofi-synthelabo

February 7, 2002

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parklawn Drive
Rockville, MD 20857

Re: *Patent Information for AVAPRO® (irbesartan)*
sNDA for The Use of Irbesartan in Patients with Hypertension
With Diabetic Renal Disease

Gentlemen:

Pursuant to the provisions of 21 C.F.R. §314.53, applicants of the sNDA for the use of irbesartan in patients with hypertension with diabetic renal disease hereby submit information on each patent that claims the drug, drug product, or a method of using the drug product and with respect to which a claim of infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use or sale of the drug product described in this sNDA.

U.S. Patent No.	Expiration Date	Type of Patent	Patent Owner
5,270,317	March 20, 2011	Drug Drug Product	Sanofi-Synthelabo
6,342,247	June 7, 2015	Drug Product	Sanofi-Synthelabo

The following party is authorized to receive notice of patent certification under §505(b)(3) and (j)(2)(b) of the Federal Food, Drug and Cosmetics Act and §§314.52 and 314.95 of 21 C.F.R.:

Sanofi-Synthelabo Inc.
Patent Counsel
9 Great Valley Parkway
Malvern, Pennsylvania 19355

The undersigned declares that U.S. Patent No. 6,342,247 covers the formulation, composition, and/or method of use of irbesartan. This product is the subject of this sNDA for which approval is being sought.

Pursuant to 21 C.F.R. §314.53(d)(2)(ii), the undersigned certifies that U.S. Patent No. 5,270,317, information for which was previously submitted in NDA No. 20-757, claims the drug and drug product which are the subject of this sNDA.

Respectfully submitted,

Michael D. Alexander
Sr. Managing Attorney,
Intellectual Property

MDA/jmh

Encl.: Duplicate copy of letter

EXCLUSIVITY SUMMARY FOR NDA # 20-757 SUPPL # SE1-021

Trade Name: Avapro Generic Name: Irbesartan Dosage Form: Tablets

Applicant Name: Sanofi-Synthelabo c/o Bristol-Myers Squibb

Approval Date If Known:

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_ __/ NO /_X__/

b) Is it an effectiveness supplement?

YES /_X__/ NO /___/

If yes, what type? (SE1, SE2, etc.) _SE1_____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X __/ NO /_ __/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three years

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / / NO /_X__/

If yes, NDA # Drug Name:

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-757, Avapro (irbesartan) Tablets

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?
YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study CV 131-048 (IDNT)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study CV131-048 _____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #[redacted] YES /_X__/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

Signature Date
Title:

Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Raymond Lipicky
1/2/02 03:17:25 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

DA/BLA # : 20-757 Supplement Type (e.g. SE5): SE1 Supplement Number: 021

Stamp Date: August 3, 2001 Action Date: February 3, 2002

HFD 110 Trade and generic names/dosage form: Avapro (irbesartan) Tablets

Applicant: Sanofi-Synthelabo c/o Bristol-Myers Squibb Therapeutic Class: 6P

Indication(s) previously approved: Hypertension

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of hypertensive patients with type 2 Diabetic Renal Disease

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
X Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo.____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.____	Tanner Stage____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed

❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

Edward J. Fromm. 1/29/02

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Avapro® (irbesartan) Tablets

Supplement to NDA 20-757

REQUEST FOR WAIVER OF PEDIATRIC STUDIES

1. NDA NUMBER

This NDA covers the irbesartan 75, 150 and 300 mg tablets. The NDA number is 20-757.

2. SPONSOR

Sanofi-Synthelabo is the sponsor of this application, and Bristol-Myers Squibb Company is the correspondent.

3. INDICATIONS

Type 2 Diabetic Nephropathy in Patients with Hypertension

4. AGE RANGES INCLUDED IN REQUEST

All pediatric group age ranges are included in this request.

5. REASONS FOR WAIVING PEDIATRIC STUDIES

Sanofi-Synthelabo and Bristol-Myers Squibb Company (BMS) are currently seeking a new indication for irbesartan in the *treatment of* adults with diabetic nephropathy due to type 2 diabetes. Currently, no clinical trials are planned to study irbesartan in the treatment or prevention of pediatric diabetic nephropathy. BMS is requesting a waiver from undertaking such a trial.

There are several reasons for requesting this waiver from the FDA: 1) Major challenges exist in the design and conduct of such a trial including a) identifying and recruiting an adequately-sized cohort of children with type 2 diabetes and established diabetic nephropathy; and b) choosing a clinically meaningful trial design. 2) Based on available epidemiologic data, the worldwide prevalence of children with overt diabetic nephropathy is very low, or progression from microalbuminuria to overt diabetic nephropathy would only occur beyond adolescence. Therefore, it would be impossible to conduct a clinical efficacy study in this population.

Cohort Identification

The absolute number of subjects available to participate in a clinical trial of pediatric subjects with diabetic nephropathy due to type 2 diabetes is very limited. Indeed, a good estimate of all available adolescents worldwide with type 2 diabetes who also have diabetic nephropathy is difficult to make given available data and this estimate may only be a few thousand. Recruiting these limited numbers of subjects in a reasonable time frame will be very difficult, if not impossible, to accomplish.

Because diabetic nephropathy takes years to develop after the onset of type 2 diabetes, only a small percentage of the children with type 2 diabetes have diabetic nephropathy before age 20. (Campagna 1999). The number with overt diabetic nephropathy by age 16 will be smaller yet, and the number who have overt disease at an early enough age to complete a trial while still no older than 16 years must be smaller still.

Type 2 Diabetes Mellitus in Pediatric Populations

The majority of diabetes in the pediatric population is not type 2 diabetes. Instead, type 1 diabetes accounts for 80% of all diabetes in children and occurs throughout childhood in all races. Only 10-20% of pediatric diabetes is type 2 diabetes, found predominantly in minority groups, such as African-Americans, Hispanics, Asians, and Native Americans. Five to ten percent of pediatric diabetes mellitus is an atypical type as found in African-American populations, and maturity-onset diabetes of the young (MODY) is seen rarely and then only in Caucasians. (Rosenbloom 1999) Type 2 diabetes is practically non-existent in neonates, infants, and toddlers. (Campagna 1999)

Only typical type 2 diabetes, as seen in a mix of minority groups, is increasing in incidence and prevalence in children. (Rosenbloom 1999) Estimates of the prevalence of type 2 diabetes mellitus for individuals aged 0-19 years are quite variable depending upon the type of study (e.g., population-based, clinic-based, case series). (Rocchini 2002) In American Indian children the prevalence of type 2 diabetes is increasing in children ≥ 10 years old (Dabela 1998); however, the reported estimates of type 2 diabetes prevalence in these children (ages 15- 19) may vary significantly depending on the reference database, ranging from as high as 5.1% in a US National Institutes of Health (NIH) database to as low as 0.46% in a database from the Indian Health Service. (Campagna 1999)

Based upon data from NHANES III, the national prevalence for all types of diabetes in the age group between 12-19 is 4.1/ 1,000. NHANES III included 2,867 individuals with blood glucose measurements between 1988 and 1994. Thirteen of the individuals sampled had evidence of diabetes – nine individuals were currently on insulin treatment, two individuals were treated with oral agents, and two individuals had blood glucose values consistent with the diagnosis of diabetes but were not being treated (newly diagnosed).

Pediatric diabetes has been described in epidemic terms (Rocchini 2002); however, the absolute number of patients between the ages of 8 and 16 with type 2 diabetes mellitus is relatively small. The U.S. Census (2000 US Census) lists approximately 14,844,317 individuals between ages 8 and 14 years, and 4,113,709 between the ages of 14 and 16 years, with a racial distribution of approximately 69.1% Caucasian, 12.1% African-American, 12.5% Hispanic, and 0.7% Native American. Assuming a prevalence rate of 410/100,000 for all cases of diabetes, and using an estimate of 26.5% for the rate of type 2 diabetes mellitus among all cases of diabetes, then the absolute number of individuals aged 8-14 years with presumed type 2 diabetes mellitus in the United States is approximately 16,128 and the number of individuals with presumed type 2 diabetes mellitus aged 14-16 years is approximately 4,469.

The number of presumed newly diagnosed patients with type 2 diabetes mellitus is even smaller. Using the aforementioned NHANES III data, the number of newly-diagnosed cases of diabetes mellitus in individuals aged 8-14 years is approximately 0.7/ 1,000. Using a rate of 26.5% for type 2 diabetes mellitus among all cases of diabetes, then the number of individuals aged 8-14 years with newly diagnosed type 2 diabetes mellitus is approximately 2,753, and for individuals aged 14-16 years the number of newly diagnosed cases of type 2 diabetes mellitus is approximately 763.

Based upon the aforementioned racial distribution from the year 2000 U.S. Census, there are approximately 241 minority patients between the ages of 14-16 years with newly diagnosed type 2 diabetes mellitus and approximately 869 minority patients ages 8-14 with newly diagnosed type 2 diabetes mellitus.

While the number of cases of youth-onset type 2 diabetes may be increasing, the overall totals remain very small. Before 1979, an NIH epidemiologic study of a primarily Pima Indian Community in Central Arizona reported only 6 cases of type 2 diabetes among Pima Indian adolescents, but as of 1996, 120 pediatric cases had been documented. Indeed, the number of cases of type 2 diabetes did increase significantly over this 17 year period, but the numbers remain small. In another report from the Indian Health Service, approximately 600,000 American Indians and Alaska natives were 0-19 years old. In this database the total number of cases of diabetes among American Indian adolescents in the Southwest increased from 128 in 1988 to 201 in 1997. (Campagna 1999)

Type 2 Diabetic Nephropathy in Pediatric Populations

The children of adult Pima Indians in Arizona, who have the highest reported prevalence of type 2 diabetes worldwide, are especially predisposed to youth-onset type 2 diabetes (Campagna 1999) and could potentially be suitable for a clinical trial in diabetic nephropathy; however, again, the absolute size of this cohort of children is quite small, (Campagna 1999) and the prevalence of diabetic nephropathy among them must necessarily be far smaller.

This last point is corroborated by a study in which 36 Pima Indians diagnosed with type 2 diabetes during childhood and adolescence were re-examined as young adults.

(Campagna 1998) After a 10 year median duration of follow-up, and at a median age of 26 years (10 years too old to finish a pediatric study, not to start it), microalbuminuria was present in only 60% (i.e., 22 of 36 people) and overt nephropathy (defined as a urine albumin/creatinine ratio ≥ 300 mg/g) was present in only 17% (i.e., 6 of 36 people).

Overall, as aforementioned, in children the reported absolute numbers for type 2 diabetes alone are very small, and overt diabetic nephropathy develops infrequently in diabetic children during childhood or adolescence. These facts render it infeasible to conduct a clinical outcome study in overt diabetic nephropathy in this population.

Trial Design Considerations

Choosing a clinically meaningful trial design to demonstrate the effect of irbesartan in pediatric diabetic nephropathy is a further challenge. With limited prospective clinical trial data available, trial design challenges include: 1) choosing a clinically meaningful endpoint which measures treatment efficacy, 2) accurately determining adequate duration of follow-up and sample size, and 3) choosing the appropriate dose or doses of irbesartan to study.

Endpoints and Duration of Follow-up

In children and adolescents, the choice of the renal endpoint as a measure of treatment efficacy is not obvious because the natural history of type 2 diabetes is not as well characterized as in adults. (Campagna 1999) Very little prospective data are available for the pediatric population which illustrate the likely course of the disease. (Dean, 1998; Pinhas-Hamiel, 1996; Scott, 1997; Fagot-Campagna, 1998) Furthermore, there are currently no established national guidelines for treatment, management, and follow-up of children and adolescents with type 2 diabetes.

In children and adolescents, as in adults, the early signs of diabetic nephropathy are usually asymptomatic, beginning with microalbuminuria (i.e., urinary albumin excretion ≥ 30 mg/day on at least two of three urine collections done in a 3-6 month period). (ADA 2001; Bennett 1995) However, microalbuminuria rarely occurs before puberty or with type 1 diabetes which is < 5 years duration (ADA 2001; Bennett 1995) A similar pattern may be expected for type 2 diabetes which begins in youth. In the NIH database, among 100 Pima Indian children and adolescents, only 22% had microalbuminuria (a urine albumin/creatinine ratio ≥ 30 mg/g). (Campagna 1998)

Although clinical endpoints similar to those seen in adults with diabetic nephropathy can be found in children and adolescents, the follow-up period to develop these endpoints may need to be very extended, thus adding to the impracticality of a study.

Sample Size

If we assume that the sample size for a study of type 2 pediatric diabetic nephropathy would need to be similar to that in IDNT or IRMA 2, the trial becomes virtually impossible given the prevalence and rate the disease progresses. Accounting for the potential to exclude some available subjects due to concomitant illnesses, we estimate that we would need to screen up to 100% of all currently existing patients worldwide for a trial in type 2 pediatric diabetic nephropathy to be successful. Even this assumes a placebo control group; if, as seems likely, this is not acceptable on ethical grounds, a low dose versus high dose trial design would require more patients still.

Dosing

To treat type 2 diabetic nephropathy in adults, the proposed recommended target maintenance dose of irbesartan is 300 mg. It may be reasonable to infer that this 300 mg dose should be studied in pediatric diabetic nephropathy, given that the pharmacokinetics of irbesartan are similar for adult and pediatric hypertensive populations (Sakarcan 2001). In fact, in adults 300 mg once daily provides nearly 100% RAS inhibition over 24 hours, but 150 mg does not.

Note, however, that the current irbesartan label suggests a maintenance dose of up to150 mg once daily for hypertensive children 6-12 years old, and up to 300 mg once daily for those 13-16 years old (US Package Insert for AVAPRO). It also states the maximum dose of irbesartan studied was 150 mg in the hypertensive pediatric population. But in light of the comments above concerning RAS inhibition, it may be problematic not to study irbesartan at 300 mg once daily, since the prevailing view concerning the mechanism of renoprotection for angiotensin converting enzyme inhibitors and angiotensin receptor blockers alike still puts efferent dilation resulting from RAS inhibition as the most likely pathway.

Thus, there is uncertainty as to the desirable maximum dose to use in a pediatric diabetic nephropathy trial.

Summary and Conclusion

Sanofi-Synthelabo and BMS are requesting a waiver from undertaking a clinical trial to study irbesartan in type 2 pediatric diabetic nephropathy. While we agree with the FDA that information on irbesartan in this population would be valuable, it appears it would be nearly impossible to find an adequate number of patients for a meaningful clinical outcome study.

Worldwide, the absolute number of pediatric subjects with both type 2 diabetes and diabetic nephropathy is limited. Recruiting these limited number of subjects in a reasonable time frame will be very difficult, if not impossible, to accomplish. Furthermore, the follow-up period for children and adolescents to develop clinically

meaningful progression of disease would need to be very extended, making such a study impractical to conduct. Finally, if the required sample size for such a study was similar to that in IDNT or IRMA 2, the trial becomes practically undoable.

Currently, there are no established guidelines for treatment, management, and follow-up of children and adolescents with type 2 diabetes. Moreover, according to the current US package insert for irbesartan (AVAPRO)) there are benefits and risks associated with the use of irbesartan for hypertension in the pediatric population. (US Package Insert for AVAPRO)

Given the currently known limited information about the natural history of youth-onset type 2 diabetes and specifically, the slow rate of progression to diabetic nephropathy in childhood or adolescence, Sanofi-Synthelabo and BMS consider it impractical to conduct a clinical outcome trial testing irbesartan for the treatment of pediatric diabetic nephropathy. We seek relief from attempting what seems all but impossible.

However, Sanofi-Synthelabo and BMS remain committed to studying the effects of irbesartan in a pediatric population with hypertension.

References

1. Fagot-Campagna A, Burrows NR, Williamson DF. "The public health epidemiology of type 2 diabetes in children and adolescents: a case study of American Indian adolescents in the Southwestern United States". *Clinica Chimica Acta.* 1999;286:81-95.

2. Rosenbloom, Arlan L., Young, Robert S., Joe, Jennie R., Winter, William E. "Emerging epidemic of type 2 diabetes in youth". *Diabetes Care.* 1999;22:345-354.

3. Rocchini AP. "Childhood obesity and a diabetes epidemic". *N Engl J Med.* 2002; 346 (11): 854-855.

4. Dabela D, Hanson RL, Bennett PH, Roumain J, Knowler WC, Pettitt DJ. "Increasing prevalence of type 2 diabetes in American Indian children". *Diabetologia.* 1998;41:904-910.

5. NHANES III.

6. U.S. Census, 2000.

7. Fagot-Campagna A, Knowler WC, Pettitt DJ. "Type 2 diabetes in Pima Indian children: cardiovascular risk factors at diagnosis and 10 years later". *Diabetes.* 1998;47(Suppl 1):A155.

8. Dean H. "NIDDM-Y in First Nation children in Canada". *Clin Pediatr.* 1998;39:89-96.

9. Pinhas-Hameil O, Dolan LM, Daniels SR, Standford D, Khoury PR, Zeitler P. "Increased incidence of non-insulin-dependent diabetes mellitus among adolescents". *J Pediatr.* 1996;128:608-15.

10. Scott, CR, Smith JM, Cradock MM, Pihoker C. "Characteristics of youth-onset noninsulin-dependent diabetes mellitus and insulin-dependent diabetes mellitus at diagnosis". *Pediatrics.* 1997;100:84-91.

11. American Diabetes Association. "Diabetic Nephropathy". *Diabetes Care.* 2001;24(Suppl. 1):S69-S72.

12. Bennett PH, Haffner S, Kasiske BL, Keane WF, Mogensen CE, Parving H-H, Steffes MW, Striker GE. "Screening and management of microalbuminuria in patients with diabetes mellitus: Recommendations to the Scientific Advisory Board of the National Kidney Foundation From an Ad Hoc Committee of the Council on Diabetes Mellitus of the National Kidney Foundation". *Am J Kidney Diseases.* 1995;25:107-112.

13. Sakarcan A, Tenney F, Wilson J, Stewart J, Adcock K, Wells T, Vachharajani N, Hadjilambris O, Slugg P, Ford N, Marino M. "Pharmacokinetics of irbesartan in hypertensive children and adolescents". *J Clin Pharmacol.* 2001; 41: 742-749.

14. US Package Insert for AVAPRO

Bristol-Myers Squibb Company

Avapro ® (irbesartan) Tablets
Supplement to NDA 20-757

DEBARMENT CERTIFICATION
UNDER THE GENERIC DRUG ENFORCEMENT ACT OF 1992

Bristol-Myers Squibb Company, based on their own information as well as information received from Sanofi-Synthelabo, certifies that neither company did not and will not use, in any capacity, the services of any person debarred under Section 306 [subsections (a) or (b)] of the Federal Food, Drug and Cosmetic Act, in conncection with this supplemental application.

Questions

Irbesartan
17 January 2002

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

The Cardio-Renal Advisory Committee is asked to opine on the benefits and risks of irbesartan, an angiotensin II receptor antagonist, for the treatment of nephropathy in type 2 diabetes. Reviews of chemistry, pharmacology, toxicology, biopharmaceutics, biometrics, and clinical safety present no apparent barriers to its approval.

The Committee is asked if it believes the strength of evidence for a treatment benefit supports approval.

The direct evidence is derived from two studies. IDNT enrolled 1715 subjects with type 2 diabetes, hypertension, proteinuria >900 mg/d, and serum creatinine between 1 and 3 mg/dL. Subjects were randomized to placebo, amlodipine 10 mg, or irbesartan 300 mg and followed for a mean of about 2 years. The primary end point was a time to first event comparison of irbesartan and placebo for death, end stage renal disease, or doubling of serum creatinine. The result was an estimated risk reduction of 20% (p=0.023), with treatment groups diverging only after about 18 months.

1. There were 411 total end point events in the placebo and irbesartan groups, 33 fewer in the irbesartan group than on placebo. One of the characteristics of a none-too-small p-value is that the result is sensitive to the handling of subjects with incomplete data.
   - 1.1 Sixteen subjects (8 on placebo or irbesartan) never received any treatment.
     - 1.1.1 How were they handled?
     - 1.1.2 How should they have been handled?
   - 1.2 Four hundred and eight subjects (275 on placebo or irbesartan) discontinued study drug.
     - 1.2.1 How were they handled?
     - 1.2.2 How should they have been handled?
   - 1.3 Nineteen subjects (13 on placebo or irbesartan) were lost to follow-up. Mortal status is known for 11/19 (7/13 on placebo or irbesartan).
     - 1.3.1 How were they handled?
     - 1.3.2 How should they have been handled?
   - 1.4 Two placebo group subjects (see page 28 of MOR) were credited with end point events for near-doubling of serum creatinine.
     - 1.4.1 How were they handled?
     - 1.4.2 How should they have been handled?
     - 1.4.3 How many other near-doubling events were *not* counted as events?
   - 1.5 In summary, what effect have the sponsor's rules for handling these situations on the credibility of the principal finding?

2. Of the 411 primary end point events on placebo or irbesartan, 58% were creatinine elevation and 42% were death or need for dialysis. All of the apparent treatment benefit was the effect on creatinine.
   - 2.1 Was this a statistical anomaly?
   - 2.2 Was this because there were just so few clinical outcome events?
   - 2.3 Was this because the effects on clinical outcome would not be expected over 57 months of follow-up?

2.4 Was this because an effect on serum creatinine is a poor predictor of clinical outcome?

2.5 Subjects who experienced doubling of serum creatinine could later have end-stage renal disease or die. When these events are counted, the relative risk of death on irbesartan was 0.92 (95% CI 0.69-1.23) and the risk of needing dialysis was 0.80 (95% CI 0.59-1.10). Are these data supportive of an effect on clinical outcome?

3. Irbesartan reduced the composite event rate compared with amlodipine by 23%.
   3.1 Considering the low nominal p-value (0.006), is this as good as a second study?
   3.2 This p-value is smaller than for the comparison between irbesartan and placebo because amlodipine did worse than placebo. How does that confirm a benefit of irbesartan?

4. Comment on other secondary end points in IDNT.
   4.1 There was a prespecified analysis of time to first cardiovascular death, non-fatal MI, CHF hospitalization, disabling stroke, or amputation. There were 416 such events, with no significant difference in the distribution among groups.
      4.1.1 Is this further evidence of a lack of clinical benefit?
      4.1.2 Is it comforting that there is a lack of apparent harm?
      4.1.3 Were there simply too few events to show a meaningful effect?
   4.2 There was a prespecified analysis of time to first cardiovascular death, non-fatal MI, coronary revascularization, CHF hospitalization, need for ACE inhibitor or ARB for heart failure, disabling stroke, amputation, or peripheral revascularization. There were 518 such events, with no significant difference in the distribution among groups.
      4.2.1 Is this further evidence of a lack of clinical benefit?
      4.2.2 Is it comforting that there is a lack of apparent harm?
      4.2.3 Were there simply too few events to show a meaningful effect?

5. Are the results of IDNT *alone* an adequate basis for approval of irbesartan for the treatment of type-2 diabetic nephropathy?

IRMA-2 randomized 611 subjects with type 2 diabetes and microalbuminuria (28 to 288 mg/day) to placebo or irbesartan 150 or 300 mg for 2 years. The primary end point was time to progression to overt proteinuria (>300 mg/day) and the analysis plan compared each active arm to placebo. The results ordered by dose, but only the 300-mg dose group was statistically significantly different from placebo.

6. Comment on the handling and implications of premature withdrawal of 166 subjects (27%).

7. There was a trend toward a *greater* increase in the rate of change in serum creatinine on irbesartan than on placebo. Comment on the hypothesized relationship between proteinuria and renal function as evidenced by creatinine clearance.

8. A 133-subject subgroup was randomized to have GFR measured at 3 months, at the end of active treatments, and then 4 weeks after the last dose. At month 3 and at the end of active treatment, there were no statistically significant differences in GFR between placebo and either dose of irbesartan. Four weeks after the last dose, GFR *increased* in all 3 treatment groups; differences from placebo were again statistically non-significant. Comment on the hypothesized relationship between proteinuria and renal function as evidenced by GFR.

9. Are the results of IDNT *plus IRMA-2* an adequate basis for approval of irbesartan for the treatment of type-2 diabetic nephropathy?

A drug with a related mechanism of action, captopril, has an indication for diabetic nephropathy in patients with type 1 diabetes. The primary basis of that approval was the demonstration, in a 409-subject, 2-year study, of 51% reduction (p=0.004) in risk of doubling serum creatinine, and a 50% reduction (p=0.006) in risk of mortality or end-stage renal disease. Both effects were manifest in the first few months of treatment. Captopril also reduces the progression for microalbuminuria to overt proteinuria.

10. Are the results with captopril germane to a discussion of irbesartan? In particular...
    - 10.1 ... is nephropathy in type 1 diabetes enough like nephropathy in type 2 diabetes?
    - 10.2 ...are the phamarmacological effects of captopril and irbesartan adequately similar?

11. If the results with captopril are relevant to irbesartan...
    - 11.1 ... are the results on protein excretion similar with respect to direction and magnitude for captopril and irbesartan?
    - 11.2 ... are the results on doubling of creatinine similar with respect to direction and magnitude for captopril and irbesartan?
    - 11.3 ... are the results on death or ESRD similar with respect to direction and magnitude for captopril and irbesartan?

12. Are the results of IDNT, IRMA-2, *and prior expectations derived from the captopril database* an adequate basis for approval of irbesartan for the treatment of type-2 diabetic nephropathy?

13. Are there results from other development programs that impact on approval of irbesartan for the treatment of type-2 diabetic nephropathy?

14. Should irbesartan be approved for the treatment of nephropathy in type 2 diabetes?

15. Do the results of the irbesartan development program in type 2 diabetic nephropathy support the use of proteinuria as a surrogate for clinical benefit?

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 20-757	Efficacy Supplement Type SE-1 (Type 2 Diabetic Nephropathy)	Supplement Number 021	
Drug: Avarpo (irbesartan) Tablets, 75, 150, and 300 mg		Applicant: Sanofi-Synthelabo-c/o Bristol-Myers Squibb	
RPM: E. Fromm		HFD-110	Phone # 594-5332
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	( ) Standard (X) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	November 6, 2002
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

KB

OCT 5 1995

Minutes
July 26, 1995
IND [redacted] irbesartan
Angiotensin II Receptor Antagonist
End-of-Phase II Meeting: for the treatment of diabetic nephropathy

Attending:

FDA:

Robert Temple, M.D.	HFD-100	Office Director (pre-meeting only)
Raymond Lipicky, M.D.	HFD-110	Division Director
Abraham Karkowsky, M.D., Ph.D.	HFD-110	Group Leader/Medical
Norman Stockbridge, M.D., Ph.D.	HFD-110	Medical Officer
Kooros Mahjoob, Ph.D.	HFD-713	Biostatistician
Granville de Oliveria, M.D., Ph.D.	HFD-110	FDA Fellow (new staff)
Kathleen Bongiovanni	HFD-111	Consumer Safety Officer

Bristol-Myers Squibb:

Sharon Anderson, Ph.D.	Director, Biostatistics and Data Management
John F. Bedard	Vice President, Worldwide Regulatory Affairs
Kenneth Given, M.D.	Senior Vice President, Worldwide Regulatory Affairs
Joan Kenney	Director, Regulatory and Health Affairs
Douglas Hay, Ph.D.	Director, U.S. Regulatory Liaison
Ken Kassler-Taub, M.D.	Executive Director, CV Clinical; Hypertension/Renal
Sol Rajfer, M.D.	Senior Vice President, Clinical R & D
Steve Freitag	Associate Director, Biostatistics

Collaborative Study Group:

Lawrence Hunsicker, M.D.	Medical Director of Organ Transplantation, Nephrology Division, University of Iowa Hospital and Clinics, Iowa City, IA
Edmund Lewis, M.D.	Professor of Medicine, Rush Medical College; Director, Section of Nephrology, Rush-Presbyterian-St. Luke's Hospital, Chicago, IL

Related submissions: Serial number 089, dated June 26, 1995

Background: Bristol-Myers Squibb (BMS) asked for this meeting to discuss their clinical development plans for irbesartan for the treatment of diabetic nephropathy. They are planning a multi-center, double-blind, placebo-controlled, randomized study in 1500-1800 patients with type II diabetes mellitus, hypertension, and proteinuria; patients will be treated with placebo, irbesartan, or amlodipine. The proposed primary endpoint is a composite of doubling of serum creatinine, end-stage renal disease, or death.

Meeting: In response to Dr. Temple's question, Dr. Given said that Bristol-Myers Squibb is not investigating the effect of captopril in patients with type II diabetes.

Dr. Temple asked whether ACE inhibitors or angiotensin receptor antagonists have an effect on

creatinine levels in non-renally impaired patients. The firm answered that ACE inhibitors do not alter serum creatinines. They cited the Modification of Diet in Renal Disease (MDRD) Study, that showed a small (1-2 ml/min) but significant difference in glomerular filtration rate, in patients treated with an ACE inhibitor.

Endpoints

Dr. Temple asked why they were planning on a combined endpoint in the proposed irbesartan study rather than an endpoint such as mortality or end stage renal disease (ESRD). The firm said that the issue is finding an endpoint that will accurately define when a patient has failed therapy, but will be ethical. By including the endpoint of doubling of serum creatinines, they believe that physicians will be able to treat their patients sooner, while they still have some renal function.

Dr. Lipicky asked why the firm did not use ESRD and mortality as the primary endpoint, with an intent-to-treat (ITT) analysis, following patients past when they would have been treated due to doubling of serum creatinines. The firm said that any intervention after the doubling of serum creatinine would be likely to alter intra-renal angiotensin levels, leading to an alteration of the course of the disease, and a curve with two components. Dr. Lipicky said that they still may beat placebo if they have patients on treatment for a year to two, altering the natural history of the disease. BMS showed a slide of the cumulative incidence of ESRD after creatinine doubling by concomitant ACE inhibitor use, from their captopril database (see attached). It shows that patients who were treated with ACE inhibitors required dialysis later on average than patients on placebo. Dr. Lipicky said that given that the administration of ACE inhibitors seems to alter the natural history of the disease, why not use clinical endpoints with an ITT analysis? The firm noted that endpoints of ESRD or mortality would be delayed, and there would be fewer events.

The firm explained that patients are scheduled to be seen every 3 months. If a patient began the study with their serum creatinine at the upper limit, e.g., 2.5 in the captopril trial (3.0 for the proposed trial), the patient may be seen at a subsequent visit and have a serum creatinine of 4.4. For this patient, doubling would be 5.0. At the next visit, 3 months later, the creatinine may have reached 5.4 and the patient may be on dialysis; in this case, the patient would have reached the ESRD endpoint and it is not possible to know the time when their serum creatinine actually doubled, by reaching 5.0. In the captopril study, patients who reached ESRD were assumed to have doubled their serum creatinines.

DSMC

Dr. Lipicky asked how long the patients will be followed. BMS answered for two years. Dr. Lipicky asked when the data would be analyzed? BMS said that the Data and Safety Monitoring Committee (DSMC) will decide whether to stop the trial early. Dr. Temple told the firm to prospectively define the parameters the DSMC would use to decide, including when and how often they will look at the data and what p value would be needed to stop the trial. BMS agreed that the criteria would be stated prospectively.

Adjunctive Antihypertensives

Dr. Temple asked what other medications would be allowed in the study to control blood pressure. The firm said that they will allow diuretics, beta blockers, and other drugs, similar

to the design used in their captopril trial. No ACE inhibitors, calcium channel blockers, or angiotensin receptor antagonists will be allowed. Dr. Temple noted that some of the allowed antihypertensives will have an effect on pre-renal function. The firm replied that may be true, but the effects should be randomly distributed. Dr. Temple disagreed, saying that the placebo group will get more adjunctive therapy. Dr. Temple asked for data on the changes to creatinine levels seen in patients treated with diuretics. The firm said that when the physician believes that a patient has reached a doubling of serum creatinine, he or she will follow a checklist to see whether the creatinine level could be elevated due to urinary tract infection, antibiotics, other medications, etc.

Secondary Endpoints

Dr. Temple asked the firm to develop a plan to describe how the secondary endpoints would be used, including what analyses would be used and what p values would mean a positive result. He said that most people would believe that a p of 0.05 would not be conservative enough, given the number of endpoints and the number of hypotheses to be tested. He suggested that they may wish to eliminate some of the secondary endpoints that they consider unimportant.

Number of Trials

Dr. Lipicky asked the firm if they are planning two trials, or if they will test the primary endpoint of this trial at between p = 0.0025 and 0.0037. He noted that unless they really make it, with a low p value, with everything going in the right direction, it may be difficult to decide to approve the indication based on one trial.

Dr. Temple asked them for information on supporting trials. He suggested that they could argue that there is a similar mechanism to the effect seen with captopril. He agreed that studies of the effect of irbesartan on proteinuria could help us come to a conclusion.

Trial Design

Dr. Lipicky noted that Dr. Karkowsky had suggested that rather than titrating all patients to the highest dose (if tolerated), they might design the trial differently to see if there is an effect with smaller doses. The firm replied that they had considered other trial designs, but since there is no evidence that the highest dose of irbesartan is poorly tolerated, and because they wish to see how irbesartan compares to amlodipine, they kept this design. Dr. Lipicky noted that if they beat placebo, they will be okay. He added that there was a choice of learning the right dose or how irbesartan compares to amlodipine, and they have chosen to learn how it compares to amlodipine. Dr. Temple added that although we want to know the right dose, there is less of a problem if there are no dose-related adverse effects; in addition, he would like to know how irbesartan compares to amlodipine. The dose of amlodipine may cause edema, which may lead to more diuretic use and greater blood pressure control. Dr. Temple noted that if amlodipine causes a lesser effect on nephropathy, it would be better to have a better blood pressure lowering effect, so that the difference could not be blamed on a lower blood pressure effect.

Number of Patients per Center

Dr. Temple asked if everyone was okay with the number of patients per center (most will have about 10 patients). There were no objections.

Revised Protocol

BMS will submit a revised protocol in response to the comments made at this meeting.

Kathleen P. Bongiovanni 10-5-95

cc:

IND [redacted]
HFD-110
HFD-111/KBongiovanni
HFD-111/SBenton

kb/8/3/95; 10/4/95 (first copy lost while circulating for review).
R/D: NStockbridge/9/8/95; AKarkowsky; KMahjoob/10/3/95.

Fromm, Edward J

From: Haffer, Andrew
Sent: Tuesday, January 29, 2002 11:16 AM
To: Fromm, Edward J
Subject: Comments on Avapro Draft Labeling

Comments on the proposed draft labeling for Avapro. These comments are based on the draft labeling submitted by BMS on 25July2001.

Lines 190-192:

Lines 196-197:

Lines 199-200:

Table 1:

Figure 3:

Lines 248-250:

Lines 275-276:

Lines 300-301:

Lines 501-502:

References:

DCRDP usually does not like to include references in the label.

APPEARS THIS WAY
ON ORIGINAL

Advisory Committee Meeting Transcripts

As of September 16, 2002, the Advisory Committee Meeting Transcripts were unavailable.